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Prevalence of Uncontrolled Hypertension in Patients With Fabry Disease

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Background: Fabry disease is a rare X-linked disease arising from deficiency of α-galactosidase A. It results in early death related to renal, cardiac, and cerebrovascular disease, which are also important outcomes in patients with elevated blood pressure (BP). The prevalence of uncontrolled hypertension, as well as the effect of enzyme replacement therapy on BP, in patients with Fabry disease is unknown.

Methods: We examined uncontrolled hypertension (systolic BP [SBP] ≥130 mm Hg or diastolic BP [DBP] ≥80 mm Hg) among 391 patients with Fabry disease who were participating in the Fabry Outcome Survey (FOS).

Results: Uncontrolled hypertension was present in 57% of men and 47% of women. In patients with chronic kidney disease (CKD) stage 1 (*n*100), median SBP was 120 mm Hg and median DBP was 74 mm Hg. In patients with CKD stage 2 (*n*172), median SBP was 125 mm Hg and median DBP was 75 mm Hg. In patients with CKD stage 3 (*n*63), median SBP was 130 mm Hg and median DBP was 75 mm Hg. There was a significant decrease in both SBP and DBP during a 2-year course of enzyme replacement therapy.

Conclusions: This study revealed a high prevalence of uncontrolled hypertension among patients with Fabry disease. Thus there is a need to improve BP control and renoprotection in patients with Fabry disease. Am J Hypertens 2006;19:782–787 © 2006 American Journal of Hypertension, Ltd.

Key Words: Blood pressure, Fabry disease, glomerular filtration rate, hypertension, reno-protection.

Fabry disease is a rare X-linked lysosomal storage disease. Deficient activity of α-galactosidase A[1] results in progressive accumulation of globotriaosylceramide (Gb_3) in blood vessels, the kidneys, and the heart.[2] In childhood, patients present with acroparesthesia, fever, angiokeratoma, hypohidrosis, corneal and lenticular opacities, and diarrhea. Later on, Gb_3 accumulation leads to end-stage renal disease, left ventricular hypertrophy, cerebrovascular disease, and premature death. In contrast to many other diseases with X-linked inheritance, most female heterozygotes are also affected because of random X-inactivation.[3,4] Patients with Fabry disease often show kidney involvement,[5] and because hypertension is an established risk factor for vascular disease and also for end-stage renal failure,[6] effective BP control is a requisite for improvement of outcome in affected individuals. Practice guidelines suggest a BP goal for patients with kidney disease of <130/80 mm Hg to prevent progression to end-stage renal disease.[6–8] Patients with an established diagnosis of Fabry disease usually have access to tertiary-level medical care.

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A list of participants in the Fabry Outcome Survey is given in the Appendix.

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Therefore optimal treatment of hypertension, including renoprotective therapy with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II–receptor blockers (ARB) or both, should be accomplished in the majority of the patients. The prevalence of uncontrolled hypertension (ie, systolic BP [SBP] ≥130 or diastolic BP [DBP] ≥80 mm Hg) in patients with Fabry disease is unknown. Our aim was therefore to analyze BP control in patients with Fabry disease.

Methods

Design

In a cross-sectional study we examined the prevalence of uncontrolled hypertension among adult patients with Fabry disease who are included in a large international database, that of the Fabry Outcome Survey (FOS).[9]

FOS

The FOS database has been approved by the institutional review board of participating centers, and all patients gave written informed consent. At the time of this analysis (March 2004), FOS contained data from 545 patients. On enrollment in FOS, each patient's medical history is documented, including the year of diagnosis of Fabry disease, signs and symptoms of the disease (cerebrovascular, neurologic, psychiatric, ear, eye, cardiac, BP, vascular, respiratory, renal, gastrointestinal, genital, musculoskeletal, dermatologic, endocrinologic, and general symptoms), treatment, demographic characteristics, and family history. Results of measurements performed routinely in clinical practice, including office measurement of BP or clinical chemistry analyses, can be entered in the database. Anonymous data are submitted electronically by participating physicians to the central FOS database.

Definition of Uncontrolled BP, Kidney Function, and Stages of Chronic Kidney Disease

We defined uncontrolled hypertension as SBP ≥130 mm Hg or DBP ≥80 mm Hg, which is the threshold for BP control in renal disease.[6,8]

For assessment of renal function, the glomerular filtration rate (GFR) was estimated using the short Modification of Diet in Renal Disease (MDRD) formula.[10] Renal function was classified according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines.[11] The definition of chronic kidney disease (CKD) was as follows: stage 1, estimated GFR (eGFR) >90 mL/min/1.73 m^2; stage 2, eGFR 60 to 89 mL/min/1.73 m^2; stage 3, eGFR 30 to 59 mL/min/1.73 m^2; stage 4, eGFR 15 to 29 mL/min/1.73 m^2; stage 5, <15 mL/min/1.73 m^2or the patient undergoing dialysis.

ERT

The enzyme α-galactosidase A is a homodimer and each monomer is composed of 398 amino acid residues and has an active site. Two aspartic acid residues in position 170 and 231 determine the catalytic reaction that releases the galactose bound to the α component of the substrate of the enzyme. Agalsidase alfa (Replagal, TKT Europe 5S/Shire Human Genetic Therapies) is a protein synthesized in a continuous line of human fibroblasts by a process of in situ activation of transcription of the *GLA* gene. The peptide sequence is identical to human α-galactosidase A. Agalsidase alfa is administered intravenously every 2 weeks in a dose of 0.2 mg/kg body weight.

Statistical Analysis

Data are given as medians (10^{th} percentile; 90^{th} percentile). We used logistic regression analysis to assess independent associations of age, sex, and renal function (eGFR) with the presence of uncontrolled hypertension of patients with Fabry disease who were not on renal replacement therapy, and provide odds ratios (OR) with corresponding 95% confidence intervals (CI).

Longitudinal follow-up of BP from baseline, to 12 months, and to 24 months of enzyme replacement therapy (ERT) was performed using individual patients' median values reported at −3 to 3 months around the start of ERT for baseline, 9 to 15 months after the start of ERT, and 21 to 27 months after the start of ERT, respectively. Statistical analyses were performed using Wilcoxon rank-sum and Kruskal-Wallis tests.

Results

Patients

Among 545 patients (463 adults, 82 children) with Fabry disease who were registered in FOS as of March 2004, a total of 391 adults (including patients undergoing dialysis and those with kidney transplants; age >18 years; 179 female and 212 male) had BP readings entered in the database. The patient distribution is summarized in a flowchart in Fig. 1. Table 1 lists demographic and clinical characteristics of the patients.

The median SBP among the 179 female subjects (median age: 43.9 [23.3; 62.3] years) was 123 (108; 145) mm

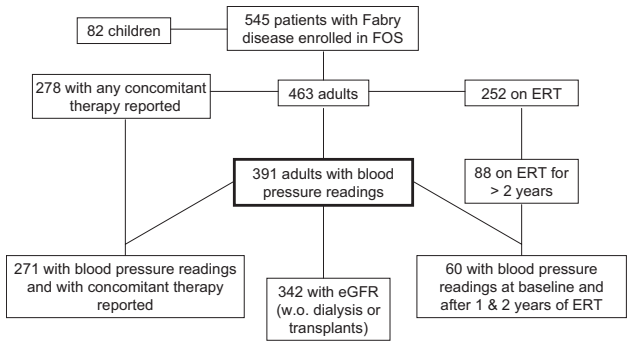

FIG. 1. Distribution of study subjects. eGFR = estimated glomerular filtration rate; ERT = enzyme replacement therapy; FOS = Fabry Outcome Survey.

Table 1. Baseline demographic data of 391 patients with blood pressure readings entered in the database and of 60 patients who had enzyme replacement therapy (ERT)

Characteristic	Patients with Fabry disease (n = 391)	Patients who received ERT (n = 60)
Sex (female)	179 (45.8)	15 (25.0)
Age (y)	40 (24, 58)	36 (23, 49)
Age at diagnosis (y)	32.0 (13, 50)	28 (13, 45)
SBP (mm Hg)	124 (110, 145)	130 (110, 150)
DBP (mm Hg)	75 (64, 85)	77 (61, 91)
Uncontrolled hypertension	205 (52.4)	40 (66.7)
Stage I hypertension	63 (16.1)	16 (26.7)
Stage II hypertension	12 (3.1)	4 (6.7)
Serum creatinine (mg/dL)	0.98 (0.77, 1.38)*	0.97 (0.80, 1.39)†
eGFR (mL/min/1.73m^2)	79 (53, 109)*	88 (49, 126)†
BMI (kg/m^2)	23 (19, 29)	22 (18, 27)

BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; SBP = systolic blood pressure.
Data are given as medians and 10th/90th centile, or as counts and frequencies.
* n = 342 (dialysis patients and transplant patients excluded).
† n = 54 (dialysis patients and transplant patients excluded).

Hg and median DBP was 75 (63; 85) mm Hg. The median SBP of the 212 male subjects (median age: 35.1 [23.1; 51.7] years) was 125 (110; 148) mm Hg and the median DBP was 76 (65; 86) mm Hg.

Of the subjects 205 (52.4%) had uncontrolled hypertension (57.1% [121/212] male; 46.9% [84/179] female).

Renal Function and BP

Among 391 patients for whom BP readings were available, GFR estimates or information on renal replacement therapy were entered into the database for 376. In patients with CKD stage I, median SBP was 120 (110; 137) mm Hg and median DBP was 74 (64; 83) mm Hg (n100). In patients with CKD stage II, median SBP was 125 (110; 145) mm Hg and median DBP was 75 (63; 85) mm Hg (n172). In patients with CKD stage III, median SBP was 130 (110; 148) mm Hg and median DBP was 75 (65; 88) mm Hg (n63). The proportion of female and male patients with uncontrolled hypertension according to eGFR class and of those who were undergoing dialysis or had received a renal transplant is indicated in Table 2.

Age (per year; OR = 1.036; 95% CI = 1.014 to 1.057) and female sex (OR = 0.576; 95% CI = 0.360 to 0.922), but not eGFR (per mL/min/1.73 m^2; OR = 0.991; 95% CI = 0.980 to 1.003) were independently associated with uncontrolled hypertension of patients who were not on renal replacement therapy (n = 342). Exluding 105 patients who used antihypertensive therapy did not materially change the results of this analysis.

Blood Pressure During ERT

Blood pressure readings were available before the start of ERT (−0.66 to 0.0 months before start of ERT), and at 12 months and 24 months of therapy with agalsidase alfa for 60 adult patients (Table 1). Uncontrolled hypertension was present in 66.7% at baseline, in 46.7% after 12 months and in 38.3% after 24 months of ERT.

The decrease in SBP and DBP after 24 months of ERT was statistically significant ($P < .05$) (Fig. 2).

Renal Function During ERT

Among the 60 patients receiving ERT for >2 years and who had BP readings entered in the database, eGFR was reported in 54 patients (three dialysis and three transplant patients excluded). In these patients the median eGFR

Table 2. Proportion of female and male patients with Fabry disease and uncontrolled hypertension according to class of estimated glomerular filtration rate (eGFR), in those undergoing dialysis and in those who had received a kidney transplant

eGFR*	Men	Women	Total
>90	37% (27/73)	33% (9/27)	36% (36/100)
60–89	60% (40/67)	50% (52/105)	53% (92/172)
30–60	67% (16/24)	56% (22/39)	60% (38/63)
<30	100% (7/7)	0	100% (7/7)
Dialysis	55% (6/11)	0	55% (6/11)
Transplant	86% (19/22)	0% (0/1)	83% (19/23)
Overall	56% (115/204)	48% (83/172)	53% (198/376)

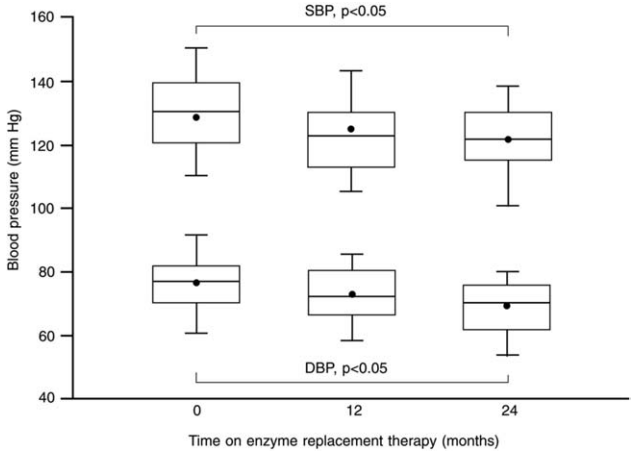

FIG. 2. Systolic and diastolic blood pressure of 60 patients with Fabry disease before, and at 12 and 24 months of enzyme replacement therapy.

remained stable during the course of treatment (88 mL/min/1.73 m^2 at baseline, 86 mL/min/1.73 m^2 after 1 year of treatment, and 84 mL/min/1.73 m^2 after 2 years of treatment).

Use of Antihypertensive Drugs in Patients With Fabry Disease

Overall the use of concomitant therapy was reported in 309 of 545 patients in the FOS database (278 of 465 adults). Of these 309 patients, 135 were reported to use antihypertensive drugs. The number of patients using different classes of antihypertensive agents is indicated in Fig. 3. Among 20 kidney transplant recipients, concomitant therapy was reported in 17 cases.

Among the 205 patients with uncontrolled hypertension, concomitant therapy was indicated in 137 patients (63 [45%] used no antihypertensive agents, 35 used one, 21 used two, and 18 used three or more different antihypertensive drugs).

Among patients with a BP < 130/80 mm Hg, concomitant therapy was indicated in 134 patients (79 [59%] patients used no antihypertensive agents, 32 used 1, 11 used two, and 12 used three or more different antihypertensive drugs).

Overall, 77 of the 309 patients were prescribed an ACEi or an ARB or both. Among the patients with an eGFR of <90 mL/min/1.73 m^2, 58 (21%) used an ACEi or ARB or both.

Use of Antihypertensive Drugs During ERT

Among the 60 patients in whom data for 24 months of ERT were available, four had no concomitant therapy entered in the database. Reports on antihypertensive treatment were available in 29 of these 60 patients, and in 10 of these patients antihypertensive treatment was started after the initiation of ERT.

Discussion

The major complications of hypertension include myocardial infarction, heart failure, stroke, and kidney failure. For instance, each increment of 20 mm Hg in SBP or 10 mm Hg in DBP doubles the risk of cardiovascular disease.[12]

From the Multiple Risk Factor Intervention Trial (MRFIT) involving 332,544 men, we know that the risk for end-stage renal disease increases continuously across the different BP categories. An SBP >210 mm Hg or a DBP >120 mm Hg confers a 22.1-fold increase in relative risk for end-stage renal disease as compared with an SBP <120 mm Hg and a DBP <80 mm Hg.[13]

Uncontrolled hypertension (BP ≥130/80 mm Hg) was present in 52.4% of our patients. A meta-analysis revealed that the prevalence of hypertension (>140/90 mm Hg) among the general European population was 44.2%,[14] and the prevalence of hypertension increases in parallel with the decline of eGFR.[11] Although the threshold for diagnosis of hypertension in the latter study of the general population and uncontrolled hypertension in our study differs, our data indicate that hypertension treatment in Fabry disease, where most of the patients are cared for by tertiary referral centers, is suboptimal. This is of particular interest, because men with Fabry disease are known to have a lifespan of approximately 50 years (about 20 years below average).[15] Among women with Fabry disease life expectancy is also significantly decreased compared with that in the general population.[3] Furthermore survival in patients undergoing dialysis is significantly shorter in those with Fabry disease than in those with other primary nephropathies.[16] The most common causes of death are renal failure and cerebrovascular events. The latter most often occur in the vertebrobasilar territory and are associated with a high recurrence rate and death.

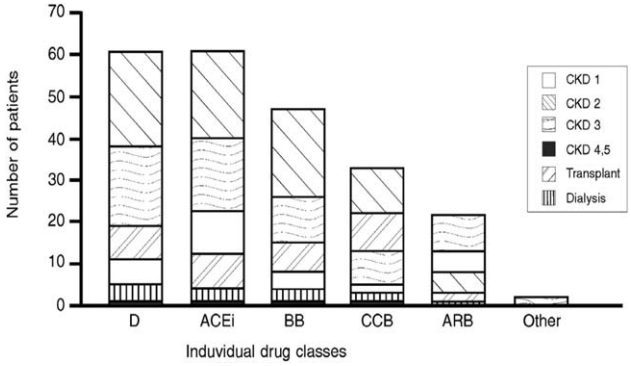

FIG. 3. Numbers of patients using individual classes of antihypertensive drugs (from 134 patients for whom antihypertensive therapy was reported in the Fabry Outcome Study [FOS]), according to chronic kidney disease (CKD) stage. ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; BB = β-blockers; CCB = calcium channel blockers; D = diuretics.

Data on hypertension or BP control in patients with Fabry disease are scarce. A group of 105 male patients with Fabry disease examined by Branton et al showed a low prevalence of hypertension (30%), and among these patients only 36% (10% of the total population) had medically controlled hypertension.[17] These data are in contrast to the results of our study, which revealed a greater overall rate of uncontrolled hypertension (57% in male patients). The age of our patients was comparable to the age at diagnosis of hypertension in the patients reported by Branton et al. However the criteria for diagnosis of hypertension differs slightly between both studies. As the largest study to date, the present analysis clearly points to a need for an improvement in the awareness of hypertension and its treatment in individuals with Fabry disease.

Enzyme replacement therapy was introduced several years ago for patients with Fabry disease.[18,19] However, hypertension was considered neither as a risk factor nor as an outcome in clinical trials of ERT.[18–21] In the present analyses of patients enrolled in FOS, BP readings were available before the start of ERT, and at 12 months and 24 months of therapy in 60 patients. Uncontrolled hypertension at baseline was present in 66.7%, after 1 year of treatment in 46.7%, and after 2 years in 38.3%. A significant decrease in SBP and DBP was also observed. This decline in the proportion of patients with uncontrolled hypertension may not be solely related to ERT, however, because 29 of the 60 patients were also receiving antihypertensive therapy. Nevertheless, in view of the high costs of ERT, improvement of BP control and renoprotective therapy is of the utmost importance for optimal use of health care resources.

The aim of antihypertensive therapy is the reduction of cardiovascular and renal morbidity and mortality. In patients with renal disease, the treatment goal is a BP of $<$130/80 mm Hg. Both ACEi and ARB have demonstrated favorable effects on the progression of renal disease. Among the patients in our cohort with eGFR $<$90 mL/min/1.73 m^2, only 58 of 276 (21%) used ACE inhibitors or ARB or a combination of these. There is therefore a need to improve antihypertensive therapy in patients with Fabry disease to achieve better outcomes.

Limitations of our study include the fact that BP readings were available in only 391 of 463 adult patients, which may suggest some selection bias. Furthermore the BP levels entered into the database by the participating FOS investigator are not validated by repeated measurements in many instances. Finally, the observation of a decrease in SBP and DBP during ERT was uncontrolled and therefore hypothesis generating.

The results of our study show that BP control and renoprotective therapy are underused among patients with Fabry disease who have a high prevalence of uncontrolled hypertension and impaired kidney function. Thus our data pave the way for future trials that should explore the potential of improved BP control on clinical outcomes in patients with Fabry disease.

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Appendix

The following investigators submitted data from their patients to the Fabry Outcome Survey (FOS) database:
Austria: O. Bodamer, A.-C. Hauser, J. Kleinert and G. Sunder-Plassmann (Vienna), and P. Kotanko, T. Kroepfl, and B. Plecko (Graz); Belgium: G. Clerbaux, B. Georges, M.C. Nassogne, and Y. Pirson (Brussels), F. Dehout, D. Roland and L. Van Maldergem (Charleroi), and K. De Smet and F. Eyskens (Middelheim); Czech Republic: J. Bultas, D. Karetová, A. Linhart, J.C. Lubanda and S. Magage (Prague); France: G. Choukroun (Amien), J. Berthelot (Anger), S. Benziane (Cambrais), B. Dussol (Marseille), P. Jaeger (Nice), R. Jaussaud (Reims), A. Khau Van Kien (Dijon), and D. Germain and O. Lidove (Paris); Germany: A. von Arnim-Baas and J. Hennermann (Berlin), HPH Neumann (Freiburg), A. Das, and S. Illsinger (Hannover), M. Beck, S. Delgado-Sanchez, C. Kampmann, K.S. Kim, S. Schwarting, H. Tremmel and C. Whybra (Mainz), B. Hoffmann and B. Koletzko (Munich), and T. Böttcher and A. Rolfs (Rostock); Italy: O. Gabrielli and I.F. Salvatori (Ancona), W. Borsini and S. Buchner (Florence), R. Parini, R. Ravaglia and S. Santus (Milan), R. Di Vito and C. Gasbarri (Ortona), A. Burlina and G. Tognana (Padova), D. Antuzzi, M. Catorina, M. Di Lillo, S. Feriozzi, and R. Ricci (Rome); Norway: L.A. Bindoff, L.H. Bostad, A.L. Grant, O.H. Haugen, A. Hirth, G. Houge, Ø. Kaarbøe, L.M. Lægreid, G. Neckelmann, E. Svarstad, T.J. Thune and C. Tøndel (Bergen), and A. Skarbøvik and A.-B. Tafjord (Ålesund); Spain: M.A. Barba (Albacete), E. Gómez Huertas and J. Herrera (Asturias), J. Ara, J. Bonal, E. Larrousse and G. Pintos (Badalona), J. Ballarin, R. Torra, J. Torras, and V. Torregrosa (Barcelona), J. González (Cadiz), M. Garcia, C. Herrera, I. Martin and J. Rodriguez (Huelva), F.J. Barbado, J. Garcia-Consuegra, A. Garcia de Lorenzo and M. López (La Paz), J. Paniagua (Ponferrada), S. Hernández (San Agustin-Linares), V. Fernández and A. León (Santiago), J. Andreu, J.A. León and E. Maya (Seville), I. Febrer and A. Perez García (Valencia) and A. Rivera (Vigo); Switzerland: P. Ferrari and B. Vogt (Bern), F. Barbey and J. Theytaz (Lausanne), and G. Schulthess, K. Walter and U. Widmer (Zurich); United Kingdom: T.M. Cox, P. Deegan, U. Ramaswami, and N. Wright (Cambridge) and A. Burns, J. Elliott, P.M. Elliott, S. Evans, L. Ginsberg, D. Hughes, A. Mehta, A. Milligan, C. Orteu (L. Richfield), and J. Shah (London).